Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 18, 20-25, 29, and 35-37 are pending in the application, with claim 18 being the independent claim. Claims 1-17, 19, and 32-34 were previously cancelled and claims 26-28, 30-31, and 40-42 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. The amendments do not allow further rejection as set forth in the present Office Action, and thus the amendments would place the case in condition for allowance or in better condition for appeal; do not raise the issue of new matter nor do they present new issues requiring further consideration or search; and do not add new claims without canceling any finally rejected claims.

Claim 24 is sought to be amended by claiming "A method of treating or ameliorating convulsions, chronic pain, or myoclonus; comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 18, or a pharmaceutically acceptable salt thereof." Excluding members of a Markush group does not violate the written description requirement. See *In re Johnson and Farnham* 194 USPQ 187 (CCPA 1977).

Claims 40-42 are sought to be cancelled and re-entered as claims 35-37. These claims were previously submitted to the Office in an Amendment and Reply Under 37 C.F.R. §1.111 dated June 4, 2008, but not considered by the Examiner. Support for claims 35-37 can be found, for example, in scheme 7, on page 31 of the originally filed specification.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Premature Final Rejection

Applicants respectfully request reconsideration of the finality of the present Office Action. According to MPEP §821.04, page 800-65, it is stated:

> If a rejoinder occurs after the first Office action on the merits, and if any of the rejoined claims are unpatentable, e.g. if a rejection under 35 U.S.C. §112, first paragraph is made, then the next Office action may be made final where the new ground of rejection was necessitated by applicant's amendment (or based on information submitted in an IDS filed during the time period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p)).

The enablement rejection under § 112, first paragraph, in the present Office action was not necessitated by an amendment or an Information Disclosure Statement submitted by the Applicants, and therefore is premature. Rather claims 24-31 were rejoined by the Examiner, and these rejoined claims are finally rejected. See also, MPEP §706.07(a), page 700-82, which makes a similar statement as quoted above. Hence, Applicants hereby request for the finality of the present Office action to be removed.

II. Rejections Under 35 U.S.C. §112

Claims 24-31 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement (Office Action, pages 3-14). Applicants respectfully traverse this rejection.

Specifically, the Examiner states that

> [t]he claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

(Office Action, page 3).

Applicants respectfully disagree. The enablement of claims 18, 20-25, 29, and 35-37 is supported by the specification as filed and publications available at the time the above-captioned application was filed for at least the following reasons.

The enablement requirement of § 112, first paragraph, ensures that one skilled in the art will be able to make and use the invention. Further, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *See* M.P.E.P. § 2164.01. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

As supported by case law, Applicants need not supply information that is well known in the art. *See In re Horwath*, 654 F.2d 103, 105-6, 210 U.S.P.Q. 689, 692 (C.C.P.A. 1981); *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d at 1366, 42 U.S.P.Q.2d at 1005 (Fed. Cir. 1997); and *In re Brebner*, 455 F.2d 1402, 173 U.S.P.Q. 169 (C.C.P.A. 1972). Moreover, one of ordinary skill in the art is deemed to know not only what is considered well known in the art but also where to search for any needed starting materials. *See In re Horwath*, 654 F.2d 103, 105-6, 210 U.S.P.Q. 689, 692 (C.C.P.A. 1981).

Further, it is well established that satisfaction of the enablement requirement pursuant to 35 U.S.C. § 112 first paragraph does not require that an Applicant make and test all species encompassed by a generic claim. *See In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976); *see also*, M.P.E.P. § 2164.06.

Given the knowledge possessed by one of ordinary skill in the art and the teachings of the present specification, only routine experimentation would have been required for making and using the compounds as claimed at the time the application was filed.

A discussion of the *In re Wands* factors follows:

1) The breadth of the claims

(a) Scope of the compounds

Regarding the breadth of the claims and further regarding the scope of the compounds, the Examiner is of the opinion that

> [c]laims 24-31 cover potentially billions of compounds of varying scope of Group I. The compounds are quinazolinone derivatives with a particular substitution and are of varying scope in the different method claims.
>
> (Office Action page 5).

Applicants disagree with the Examiner's assertion that the breadth of the claims is so large so as to render the claims non-enabled.

While the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'," not everything necessary to practice the invention need be disclosed. *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court

stated that a "demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts." Accordingly, an inventor need not be limited to claiming only those materials and processes which will work and need not disclose what is well-known and is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The pending claims disclose substituted quinazoline compounds. Examples 1-109 as provided in pages 40-92 of the specification are illustrative of the methods to prepare a vast array of substituted quinazoline derivatives. Further examples 110a and 110b illustrate the biological activity of compounds listed in Table 1, pages 95-97 of the specification. The data demonstrate activity in "inhibiting or modulating AMPA receptors expressed in oocyte and anticonvulsant activity against maximal electroshock induced convulsion" for representative compounds (page 94, lines 3-5). Accordingly, the specification discloses exemplary compounds useful for practicing the claimed methods and assays by which to test their activities. Moreover, the data demonstrate a reasonable correlation between AMPA antagonist activity and the anti-convulsant activity; and the data demonstrates such activity across the entire scope of the claims.

(b) Scope of the diseases covered

Regarding the breadth of the claims with respect to the scope of the diseases covered, the Examiner is of the opinion that the diseases covered in claims 24-31 are not enabled by the disclosure. (Office Action page 6).

Specifically, the Examiner rejects the term "preventing" in claim 24 in that "the disclosure does not teach how to identify a host with the potential to develop such conditions/diseases or how to provide preventive measure to the identified host." (Office Action page 6). Applicants have amended claim 24 to replace the phrase "A method of treating, preventing or ameliorating" with "A method of treating or ameliorating". Furthermore, solely to advance prosecution of the captioned application, Applicants have amended claim 24 by narrowing the scope of the claim to treating or ameliorating convulsions, chronic pain, or myoclonus.

2) Direction and Guidance

The Examiner asserts that the direction and guidance "provided in the specification is very limited. The dosage range information is meager at best. It is generic; the same for all diseases/condition claims 24-31 covers." (Office Action page 10).

Applicants respectfully disagree. Applicants refer to pages 35-37 of the specification. Administration of the compound can be given orally, rectally, or via injection. Oral forms of administration can be tablets, dragees, or capsules while rectal forms can be suppositories. Injections can be given intramuscularly or intravenously. Dosage ranges are also discussed, for example, to treat chronic pain or convulsions "a

unit dosage level of from about 0.01 to about 50 mg/kg of body weight, or an equivalent amount of the pharmaceutically acceptable salt thereof, on a regimen of 1-4 times per day." The specification provides ample guidance concerning the dosage range related to the treatment or amelioration of chronic pain or convulsions. There is no reason to doubt that similar dosages would work for treating myoclonus.

Furthermore, references disclosed in the specification (p. 3, lines 16-23), which were submitted in an Information Disclosure Statement filed June 4, 2008, provide guidance and direction for the amended claimed invention. More specifically, Copani, *et al.*, *J. Neurochem. 58*:1199-1204 (1992) (IDS Document AT2), teaches that piracetam "was found to be a positive modulator of AMPA receptors". A clinical study demonstrated that piracetam was effective in treating patients with myoclonus (Ikeda *et al.*, *Movement Disorders 11*:691-700 (1996)) (IDS Document AR5). These two references taken together demonstrate guidance to one skilled in the art to use the claimed compounds to treat or ameliorate myoclonus.

Further guidance to support the use of the claimed compounds to treat or ameliorate convulsions can be found in the specification, on page 4, lines 3-5. De Sarro *et al.*, *Eur. J. Pharmacol. 294*:411 (1995) (IDS Document AR3) demonstrated that GYKI 52466, an AMPA antagonist, has "been shown to be an effective anticonvulsant". Further on page 4, lines 20-23, LY300164, an AMPA antagonist, has been demonstrated by Anderson *et al.*, *J. Am. Chem. Soc. 117*:12358-12359 (1995) (IDS Document AR1) to have anticonvulsant activity. Furthermore, on page 35, lines 9-11, U.S. Patent No. 5,514,680 (IDS Document AD1) teaches that "anticonvulsant efficacy of the AMPA antagonists may also be assessed in the pentylenetetrazol (PTZ)-induced seizure test."

Additionally, the references to support treatment or amelioration of chronic pain can be found in the specification, page 4, lines 15-19, where Sang *et al., Soc. Neurosci.* Abstract #401.14, 1997 (IDS Document AR8) showed an effective compound which blocked "the sensitization in the spinal neuron that mediates capsaicin-evoked allodynia and hyperalgesia in human (sic), a human model of chronic pain." Further support in the specification is also described on page 35, lines 12-15, which exemplifies how "AMPA receptors are involved in pain transmission and the development of persistent pain following nerve and tissue injury." Reference is made to U.S. Patent No. 5,514,680.

Lastly, guidance and direction are provided by the working examples. The *in vitro* electrophysiological assay described in the specification, page 34, lines 28-29, to page 35, lines 1-8, and further in examples 110a and 110b, pages 93-94, along with corresponding Table 1, pages 95-97, provides data, which demonstrate the AMPA antagonist and anticonvulsant activity of selected compounds. As stated in the specification, page 94, lines 2-5, "[p]otencies of selective compounds described above in inhibiting or modulating AMPA receptors expressed in oocyte and their anticonvulsant activity against maximal electroshock induced convulsion are shown in Table 1." This data provides support to lead one skilled in the art to deduce administering the claimed compounds to treat chronic pain and myoclonus.

It is respectfully submitted that the guidance provided in the specification is sufficient to enable one of ordinary skill to practice the invention without undue experimentation. Applicants respectfully submit that there is no issue of undue experimentation as it relates to working examples and making compounds of the present invention.

3) Nature of the invention and predictability in the art

Regarding the nature of the invention, the Examiner is of the opinion, "[t]he invention is directed toward medicine and is physiological in nature. The invention is directed toward therapeutic use of the claimed compounds in treating/preventing/ameliorating all the recited diseases/conditions in claims 24-31." (Office Action page 9).

The amended claims are directed to the use of substituted quinazolines and to treat a narrow group of diseases/conditions; specifically, convulsions, chronic pain, and myoclonus. The invention is directed toward medicine and is physiological in nature.

Regarding the level of predictability of the art, the Examiner is of the opinion, "Applicants do not provide highly predictive competent evidence or recognized tests to prevent, treat or ameliorate all diseases/conditions recited for the claimed compounds of varying scope of Group I. Pharmacological activity in general is unpredictable." (Office Action page 9). Applicants respectfully disagree. According to MPEP §2164.03, page 2100-197, it states that

> [t]he predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.

As described in the above section, "Direction and Guidance", there are ample references along with working examples provided in the specification to allow one skilled in the art to predict the use of the recited compounds to treat or ameliorate convulsions, chronic pain, or myoclonus.

4) State of the Prior Art

Regarding the state of the prior art, the Examiner states "the state of the art indicates a need for undue experimentation." (Office Action page 10). Not in acquiescence in the propriety of the rejection, but rather solely to advance prosecution, claim 24 has been amended and claims 26-28 and 30-31 have been cancelled. Applicants have amended the scope of the diseases/conditions covered by claim 24 to treat or ameliorate convulsions, chronic pain, or myoclonus. Enablement of the narrow scope of the recited diseases/conditions is supported by the prior art cited by the Examiner.

However, the Examiner did cite a reference, De Sarro, *et al.*, *Current Topics in Med. Chem 5*: 31-42 (2005), which "emphasized the need for combined agents in anticonvulsant therapy." (Office Action page 12). Applicants respectfully disagree. Anticonvulsant activity is deduced in Examples 110a and 110b. See arguments under section, "Direction and Guidance" above. The compounds tested were not administered in conjunction with another agent.

5) Working Examples

Regarding the working examples, the Examiner asserts that "the specification working examples do not show *in vivo* treatment of all recited diseases/conditions." (Office Action page 13). Applicants respectfully disagree. See Applicants argument under section, "Direction and Guidance". Briefly, Applicants refer the Examiner to the

specification, Example 110a and 110b, pages 93-97, and description of the experimental methods on page 34-35, lines 28-29, 1-8.

Furthermore, the Examiner states "[n]o examples show prevent/treatment/amelioration of diseases/conditions as the claims recite in 'an animal'." Applicants amend claim 24 to replace the phrase "an animal" with "a mammal". The *in vitro* experimental methods described in the specification page 34, lines 28-29, and page 35, lines 1-8, demonstrate that mice were used to test the anticonvulsant activity of the AMPA antagonists.

6) Skill of those in the art

Regarding the skill of those in the art, the Examiner is of the opinion that, "[t]he articles discussed above demonstrate that enablement was not established for the claimed methods as of the filing date." (Office Action page 14). As stated previously, Applicants have amended claim 24 to narrow the scope of the diseases/conditions being treated or ameliorated by the claimed compounds. Applicants also refer the Examiner to the arguments listed under the section, "Direction and Guidance".

7) Quantity of experimentation needed to make or use the invention

Regarding the quantity experimentation needed, the Examiner is of the opinion, "one skilled in pharmaceutical arts would have an undue burden to make and use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use." (Office Action page 14).

Weighing factors 1-7 with respect to the presently claims method, it is clear that undue experimentation is not required to practice the claimed invention. It would require routine experimentation for one skilled in the art to practice an embodiment of the claimed invention based upon the detailed teachings regarding the manner of making and using the particular substituted quinazoline compounds to treat or ameliorate one of the three conditions falling within the scope of the claims.

In view of the above, it is respectfully requested that the rejection of claims 24-25, 29, and 35-37 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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